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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,460	09/28/2006	Yoko Yamagata	56861	9304

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EXAMINER	
BURKHART, MICHAEL D	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
02/18/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,460	YAMAGATA ET AL.	
	Examiner	Art Unit	
	Michael Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-9 and 14-23* is/are pending in the application.

4a) Of the above claim(s) *5,6 and 14-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2, 7-9 and 18-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt and entry of the amendment dated 11/9/2009 is acknowledged. After entry of the amendment, claims 1, 2, 5-9 and 14-23 are pending.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 103

Claims 1, 2, 7-9 and 18-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elgersma et al (Neuron, 2002), Wang et al (PNAS, 2003), Hanson et al (Neuron, 1994) and Sutoo et al (Brain Res., 2002). **This rejection is maintained for reasons made of record in the Office Action dated 7/9/2009, and for reasons set forth below.**

Claims 18-23 are new, and recite a specific lysine residue "adjacent to the ATP-binding site in the catalytic domain of CaMKIIα" has been substituted. A review of the specification indicates this residue to be that found at position 42 of CaMKIIα, i.e. K42 (see ¶'s [0041]-[0043] of the published application, US 20070050858 A1), and this residue number is recited in claims 20 and 23. This is the very residue, and substitution mutation(s), taught by Hanson et al, i.e. the K42M or K42R catalytic domain mutants (page 3 of the Office Action dated 7/9/2009).

Response to Arguments

Applicant's arguments filed 11/9/2009 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) Wang et al do not teach knock in mice; 2) Elgersma et al do not teach a knock-in animal using an inactive CaMKIIα according to the

claims; 3) the knock-in mice and cells of the claims cannot be produced easily by using the K42 mutations taught by Hanson et al with the techniques of Elgersma et al; 4) the interpretation of Sutoo et al set forth by the Examiner has a major flaw, and thus the limited effects of the claimed mutants on various CNS areas are unexpected.

Regarding 1), Wang et al teach the creation of knock-in animals comprising mutant CaMKIIα genes (page 4292, first column, first full ¶) for reasons of record and despite applicants protests to the contrary.

Regarding 2), Elgersma et al was not relied upon to teach these claim limitations. The T305D mutation of Elgersma et al is taught to be persistently phosphorylated (and thus inhibited), but to likely not bind Ca^{2+}/calmodulin. See the abstract and ¶ linking the first and second columns, page 494. This appears to be a moot argument because the mutations of Elgersma et al are in the calmodulin binding domain of CaMKIIα, and thus lie outside the scope of the claimed mutations in the catalytic domain.

Further regarding 1) and 2), in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Regarding 3), the concept and techniques for targeting literally any given gene for a knock-in mutation were known to the skilled artisan at least by the time of Elgersma et al (e.g. Mak et al, 2001 and Giese et al, 1998, of record), as was the sequence and structure of the CaMKIIα gene (see Colbran et al, 2004, of record, in particular, Fig. 1). Hanson et al describe precisely how to generate the substitution mutations (p. 953, second column, first full ¶). That

the CaMKIIα gene may be large (applicants have not provided a copy of the Nishioka et al reference they rely upon, hence any teachings within have not been considered) is not disputed at the moment, but this does not set it apart from literally any other mammalian gene targeted for a knock-in mutation, as such genes also comprise various numbers of exons and introns. Applicants assertion is unsupported by any facts or reasoning and is contradicted by the successful gene targeting methods taught by the totality of the prior art. There appears to be no need to target both exons 2 and 12 of the CaMKIIα gene as applicants insist: why would the skilled artisan, when introducing a substitution into exon 2, also target exon 12? Applicants are inventing a problem that does not exist in the prior art.

Regarding 4), the interpretation of the Sutoo et al reference stands. The claim is broadly worded such that only "neuronal activity" must be affected (not CaMKIIα expression, as applicants appear to argue), and this limitation is only found in claim 2. Applicants have not provided the "Yamagata Declaration" referenced in their arguments, nor the "Carpenter's Human Neuroanatomy", thus, any teachings and assertions from these documents are not of record and have not been considered. Applicants appear to want a 35 USC 102 level of disclosure in the prior art whereas this is a 35 USC 103 rejection. There is always some unpredictability about the outcome of complex experiments, particularly those involving *in vivo* results such as this case. However, there is no technical burden to the creation of the mice (and cells) in the first place, nor in the assessment of the phenotype. Ample motivation to create the mice and cells has been provided and has not been disputed. Given the totality of the prior art teaching that CaMKIIα has a prominent role in neuronal activity and learning, it is not surprising that such a complex and broadly worded phenotype as "neuronal activity" is affected in certain areas of the brain but

not others. The activity of CaMKIIα can be partially supplemented by CaMKIIβ (Giese et al, page 870, middle column). This may explain why differential effects are found in certain areas of the brain when the claimed mutants are used, or it could be that CaMKIIα is not required for the measured "neuronal activity" in the cerebral cortex and striatum even though it may be highly expressed in these regions. An example of an unexpected result from using the claimed mice would be that no affects on neuronal activity were found in any part of the CNS, as this would contradict the teachings of the prior art.

Double Patenting

Applicant is advised that should claims 18 or 21 be found allowable, claims 20 and 23 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claims 18 and 21 already recite "the lysine residue adjacent to the ATP-binding site", and as there appears to be no other lysine residue in the CaMKIIα sequence that can reasonably be considered to meet this limitation, reciting Lys-42 in claims 20 and 23 does not alter the scope of claims 18 or 21, respectively.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Burkhart whose telephone number is (571)272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Burkhart/
Primary Examiner, Art Unit 1633